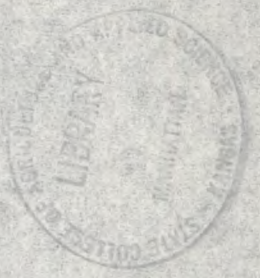
THE STRUCTURE PROOF OF AZIPYRAZOLE

by

WILLIAM ROBERT HINE, JR.

B. S., Beloit College, 1954



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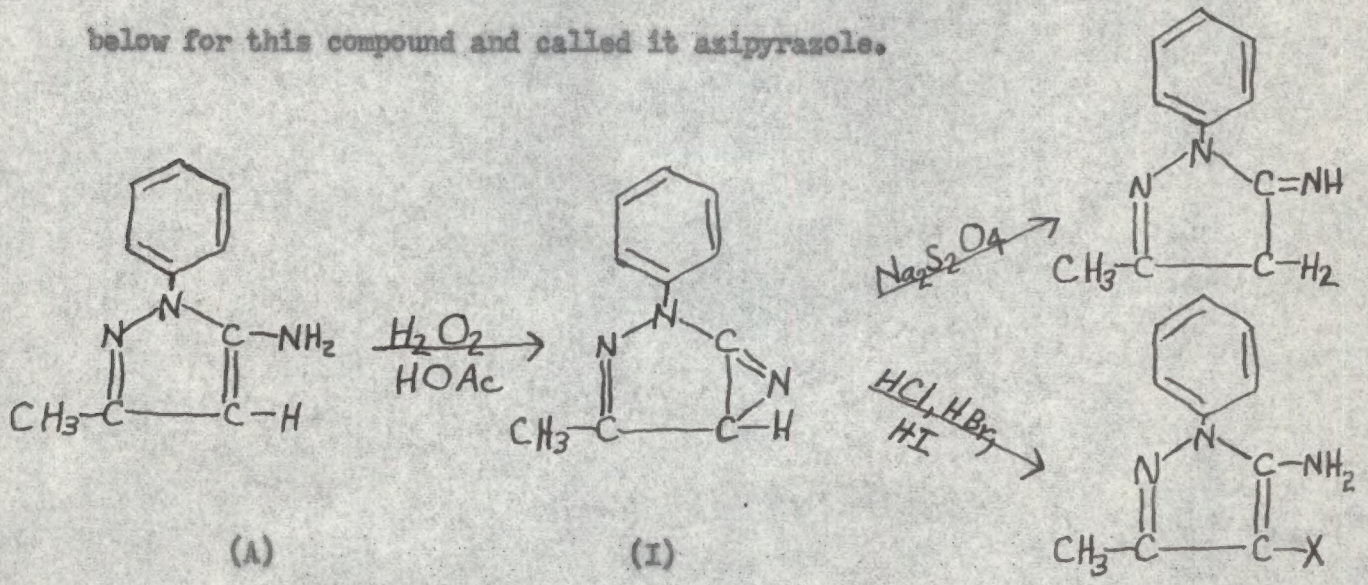
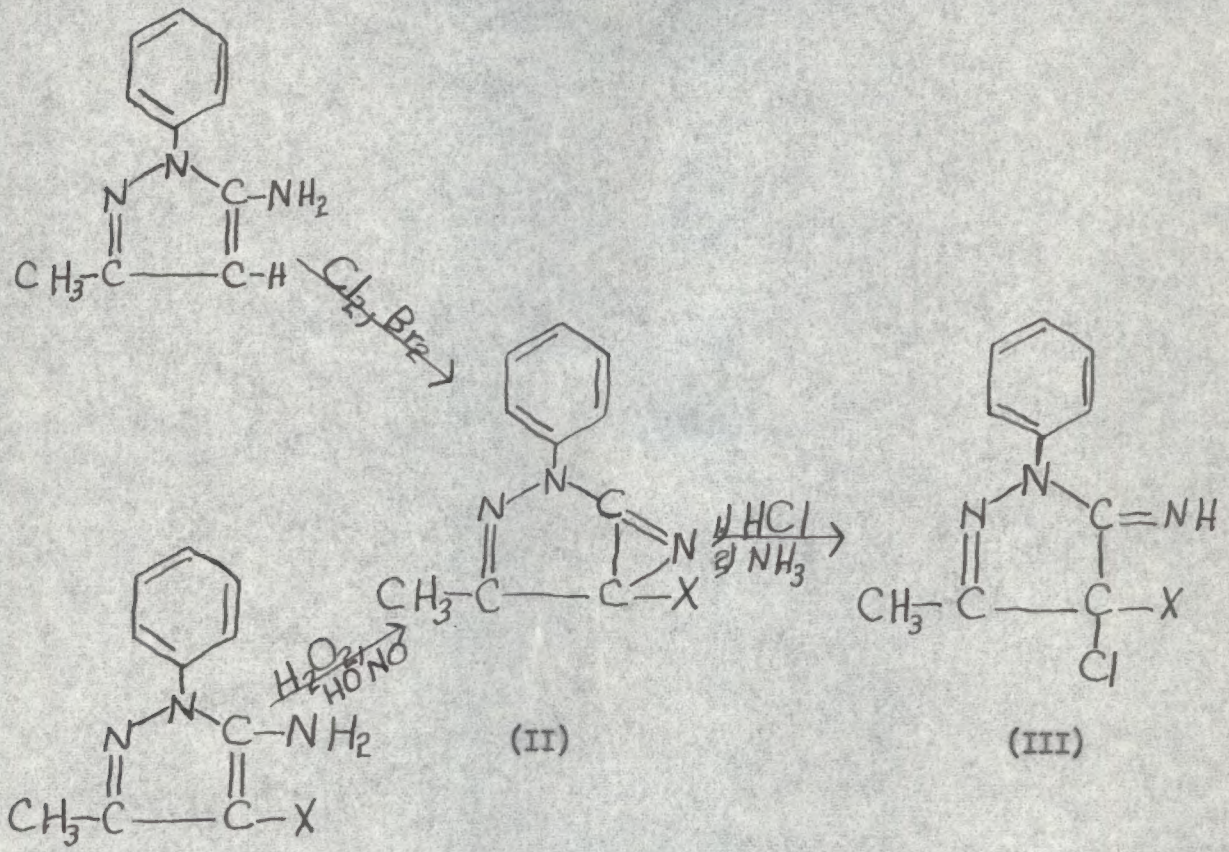
HISTORICAL

In connection with work on the well known drug antipyrin, Michaelis and Brust (9) in 1904 attempted to diazotize 3-amino-5-methyl-2-phenylpyrazole (A). The product isolated was not the expected pyrazolone, but rather was a brown crystalline material melting at 109°C and according to analysis containing two less hydrogen than the starting material. The corresponding 4-halogen derivative was also prepared by treating 3-amino-5-methyl-2-phenyl-4-halogeno-pyrazoles with excess halogen or nitrous acid. At this point work was discontinued. However, some years later, in 1913, Michaelis and Schafer (11) reported that 3-amino-5-methyl-2-phenylpyrazole reacted vigorously with hydrogen peroxide in acetic acid solution to form the same product as from the diazotization. The carbon, hydrogen, nitrogen analysis and molecular weight determination showed this material to contain two less hydrogens than the starting material. When boiled in a sodium hydrosulfite solution, it was converted to a tautomer of the starting pyrazole. When warmed with concentrated hydrogen halide acids, (A) gave 3-amino-4-halogeno-5-methyl-2-phenylpyrazole. From this data, Michaelis and Schafer (11) proposed the structure (I) shown below for this compound and called it azipyrazole.

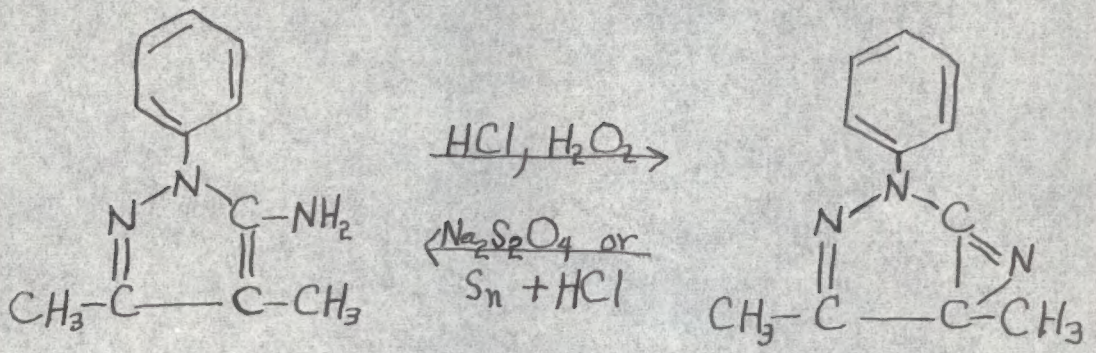


(A) (I)

These authors also found that halogenated azipyrazoles (II) could be prepared by the reaction of chlorine, bromine, or bleaching powder on 3-amino-5-methyl-2-phenylpyrazoles (Michaelis and Schafer, 11). Furthermore, (II) could be prepared by treating 3-amino-4-halogeno-5-methyl-2-phenylpyrazoles with nitrous acid or hydrogen peroxide. When (II) was dissolved in hydrochloric or hydrobromic acid, and then treated with excess ammonia, a new product, 4,4-dihalogeno-3-imino-5-methyl-2-phenylpyrazole (III) was formed.



A methyl homolog of azipyrazole (IV) was also prepared by treating 3-amino-4,5-dimethyl-2-phenylpyrazole in hydrochloric acid solution with hydrogen peroxide (11). It was again found as in the case of (I), that (IV) could be converted back to the starting pyrazole by sodium hydrosulfite or tin and hydrochloric acid.



(IV)

STATEMENT OF THE PROBLEM

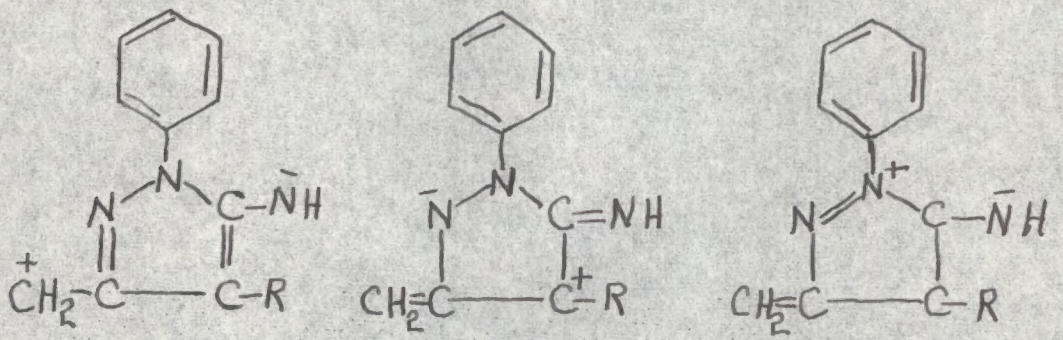
The structures proposed by Michaelis and his co-workers for azipyrazole are satisfactory as far as explaining the reactions with hydrogen halides and reducing agents. However, other factors must be considered that make the structure improbable.

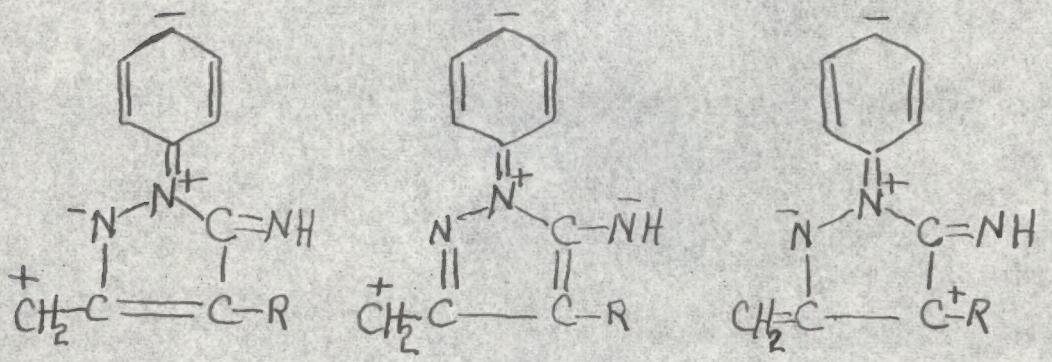
In the structure proposed by Michaelis, a fused three membered ring was formed with a double bond at the bridgehead in the bicyclic system. Such a system would be highly strained as can be shown by the models and in addition would violate Bredt's Rule. Another objection to the proposed structure arises from the behavior of azipyrazole during synthesis involving free chlorine or bromine. Normally, it would be expected that the C_6H_5N group would act like aniline in the presence of halogen. If this were the case, halogenation of the benzene ring would be expected, but this was not observed.

The difficulty in explaining the above facts led to an attempt to prepare azipyrazole and to then study the compound and determine its true structure.

DISCUSSION

At the start of this work, it seemed a likely structure for azipyrazole was one of the meso-ionic type proposed by Baker, et. al., (2) and his co-workers in connection with their work on sydnones. These workers were able to show that the physical and chemical properties of the sydnones could best be explained by considering the structure to be a resonance hybrid. By similar reasoning, it was thought that the effect of oxidizing agents on 3-amino-5-methyl-2-phenylpyrazoles could be explained as a removal of one hydrogen from the amino group and one hydrogen from the methyl group. The resulting product, azipyrazole, would then be stabilized by many resonance forms rather than by the formation of a new ring. Some of these resonance forms are:





(R H, CH_3, halogen)

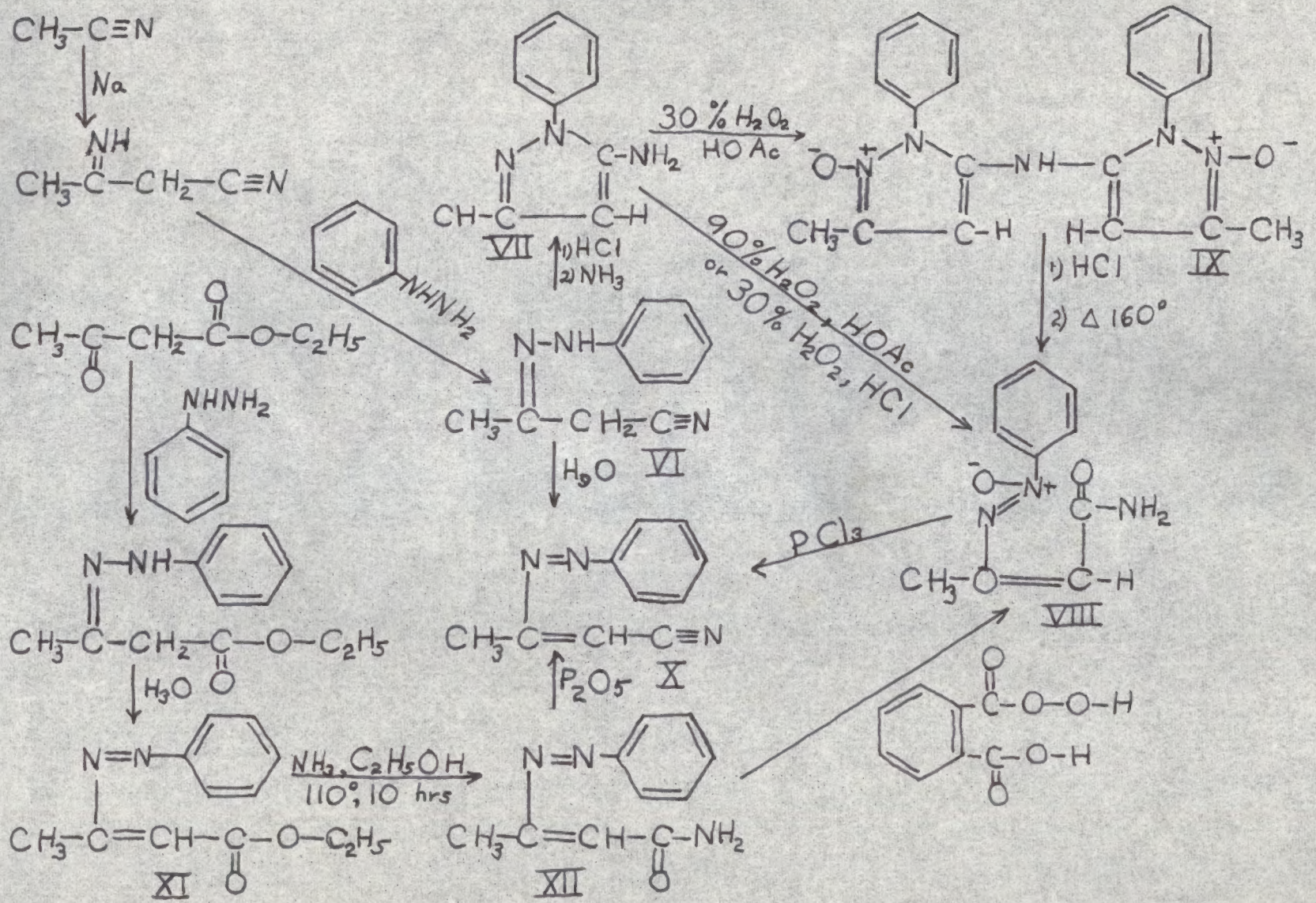
As Baker pointed out in connection with the work on sydnones, the C_6H_5N group would not act like aniline, and this would explain the unexpected reaction of azipyrazole with the halogens.

Baker further pointed out in the work on sydnones, that a compound with a meso-ionic type structure would have a high dipole moment. Therefore, if azipyrazole was of this type structure, a high dipole moment was to be expected.

The method used for preparing azipyrazole was that of Michaelis and Schafer (11) in which they ran a Thorpe reaction on acetonitrile. The condensed product, diacetonitrile (V), was treated with phenylhydrazine to give the diacetonitrile phenylhydrazone (VI) which was then cyclized by hydrogen chloride gas. The cyclic hydrochloride was treated with gaseous ammonia to give 3-amino-5-methyl-2-phenylpyrazole (VII). When (VII) was treated with 30 per cent hydrogen peroxide in acetic acid solution as described by Michaelis and Schafer, a white crystalline solid mp. 229-230°C was obtained, but no azipyrazole as described by Michaelis was found. Hydrochloric acid was tried in place of acetic acid as the solvent and from this was isolated a brown material which when dissolved in ether and then allowed to evaporate, gave long brown needles mp. 113°C. This brown solid was also obtained by treating the white solid with hydrochloric acid and then heating the mixture at 160°C. Furthermore, if (VII) was treated with 90 per cent hydrogen peroxide in acetic acid solution, the brown compound was once again obtained.

It was assumed that the brown compound was the azipyrazole described by Michaelis but in a more pure form because of the somewhat higher melting point. Therefore, dipole moment studies were run on a benzene solution of this compound. The results obtained gave a dipole moment of .86 Debye units, a very

FLOW SHEET OF REACTIONS



low value indeed, and indicated that the compound was not of the meso-ionic type described by Baker to have a high dipole moment.

However, to further test this conclusion, Kuhn-Roth C-Methyl values were determined using the procedure described by Eisenbraun, et. al., (6). If the azipyrazole was of the meso-ionic type, the C-Methyl value would be low since the methyl group is involved in the resonance forms. However, the values obtained were very nearly one, indicating the presence of one methyl group.

Table 1. C-Methyl and Molecular Weight Data

Compound	Amount Used in Determination (in mg.)	C-Methyl Number	Number of CH_3 Groups	Molecular Weight
brown compound (mp. 113 C)	17.3	.942	1	
	18.5	.987	1	188
	17.9	.963	1	
white compound (mp. 229-230 C)	17.4	1.66	2	
	16.1	1.7	2	388.8
	17.7	1.7	2	
3-amino-5-methyl-2-phenylpyrazole	19.4	1.03	1	
	16.9	1.05	1	

From this data, it was concluded that the brown material was not of the meso-ionic type structure.

An infra red spectrum of this brown compound was taken and the following bands were found: one each at 2.96μ and 3.15μ characteristic of the N-H stretching of an amide, one at 5.95μ characteristic of the carbonyl of an amide, one at 6.164μ characteristic of a conjugated carbon-carbon double bond, a band at 6.22μ assigned characteristic of an azo linkage, one each at 6.83μ

and 13.06 μ which were not at once assigned, one at 11.93 μ characteristic of a $R_1R_2C=CH_2$ type carbon-carbon double bond and the other bands normally expected for carbon-hydrogen, aromatic carbon-carbon and carbon-hydrogen, and carbon-nitrogen. Significantly, bands at 6.80 μ and 10.70 μ were absent which according to Rondestvealt and Chang (16) were characteristic of the pyrazole ring.

A carbon, hydrogen, nitrogen analysis was obtained and indicated an empirical formula of $C_{10}H_{11}NO_2$. The molecular weight determined by the Rast method to be 188, which is in fair agreement with this formula (theoretically would be 205). (Table 1). One of the two oxygens would be accounted for by an amide group. The other oxygen could not be involved as an alcohol, ketone or aldehyde since there were no infra red bands found for these groups. A possibility was that the oxygen was involved in an $\overset{+}{N}-\bar{O}$ group because it was formed by reaction with hydrogen peroxide in acetic acid. It will be recalled that pyridine-N-oxides are prepared with hydrogen peroxide in acetic acid (Ochiai, 14).

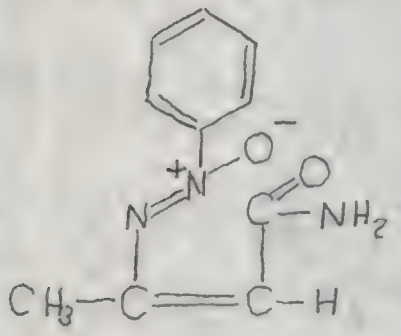
It was found that no infra red information was available concerning the $\overset{+}{N}-\bar{O}$ type of band. A calculation was made by Dr. Basil Currette of the Physics Department at Kansas State College on the vibration of pyridine-N-oxide, and he predicted bands for the $\overset{+}{N}-\bar{O}$ group at 1500 $\pm$ 200cm.$^{-1}$ (6.67 μ - 7.69 μ), 700 $\pm$ 100cm.$^{-1}$(12.8 μ - 14.7 μ) and 300 $\pm$ 30cm.$^{-1}$ (16.2 μ - 22.2 μ). This was tested experimentally with pyridine-N-oxide obtained from Reilly Tar and Chemical Company and bands at 6.82 μ, 12.9 μ and 16.9 μ were found which were not in the pyridine spectrum. The spectra of additional N-oxides were examined and the results are shown in Table 2.

Table 2. Infrared Absorption Bands

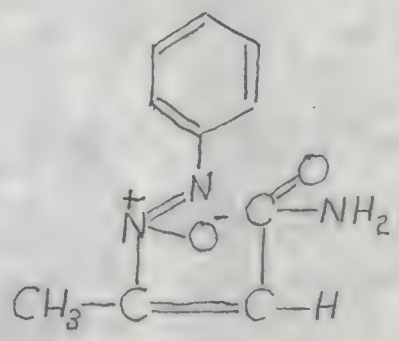
Compound	Band observed not in corresponding compound without N-oxygen		
pyridine-N-oxide	6.82 μ	12.9 μ	18.9 μ
2-picoline-N-oxide	6.83		
4-picoline-N-oxide	6.87		
2,6-lutidine-N-oxide	6.87		
azoxybenzene	6.77	12.99	19.12

From these data, it seemed quite certain that the bands at 6.83 μ and 13.46 μ in the brown compound could be attributed to the $\overset{+}{N}-\overset{-}{O}$ group.

This evidence is compatible with two possible structures for the brown compound, (VIII) and (VIII A).



(VIII)

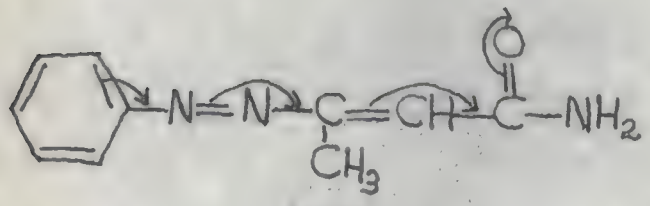


(VIII A)

It seemed reasonable to consider the oxygen on the α-nitrogen also because the compound was vinylogous to benzenesoformamide, for which Angeli (1) reported the α-oxide structure. His evidence, however, is actually not decisive since it was based on the observed deactivation of the ring towards

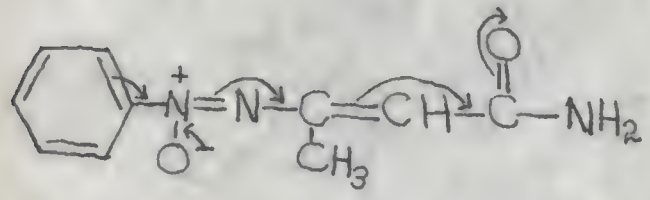
chlorination. The $\overset{+}{N} - \overset{-}{O}$ structure should be strongly deactivating also, but no comparison was made with the rate of chlorination of benzanilide.

The α-oxide structure assigned here, however, was based on both ultra violet and infra red spectral studies. The maximum for the near ultra violet band of the amide (XII) occurred at 251mμ while that for the amide-1-oxide was at 241mμ. This shift to shorter wave length indicated the less conjugation of the benzene ring in the latter compound, which is to be expected from an α-oxide. The resonance in the amide involving the benzene ring,



(XII)

would be greatly lessened by an oxide function on the α-nitrogen, since the oxygen would compete with the benzene ring to supply electrons to the carbonyl group. Note that it cannot supply electrons to the ring itself.



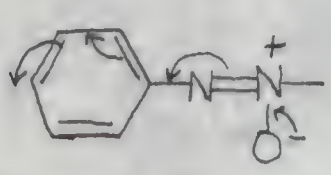
(VIII)

The amide function at the β-nitrogen, however, should have the opposite effect, since it can conjugate with the benzene ring, yet would not interfere with the amide-benzene ring conjugation.

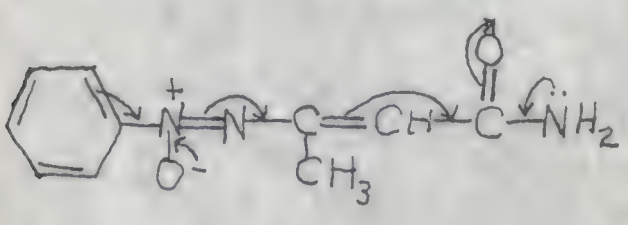

.750
.700
.650
.600
.550
.500
.460
232
235
240
245
250
255
I
II
I = 3-(benzeneazoxy)-crotanamide
II = 3-(benzeneazo)-crotanamide

Therefore, with this structure a shift towards longer wave lengths would be expected.

The infrared spectrum of 3-(benzeneazoxy)-crotonamide contained the $\overset{+}{N}-\overset{-}{O}$ band at 6.81μ, as compared to 6.77μ for azoxybenzene. Since this is the stretching vibration, it was obvious that the band is somewhat stronger in the azoxybenzene. If (VIII) was of the β -oxide structure, it would be expected that the band would be very nearly the same as in azoxybenzene and of similar strength, because the $\overset{+}{N}-\overset{-}{O}$ bands would be the same type of hybrid.

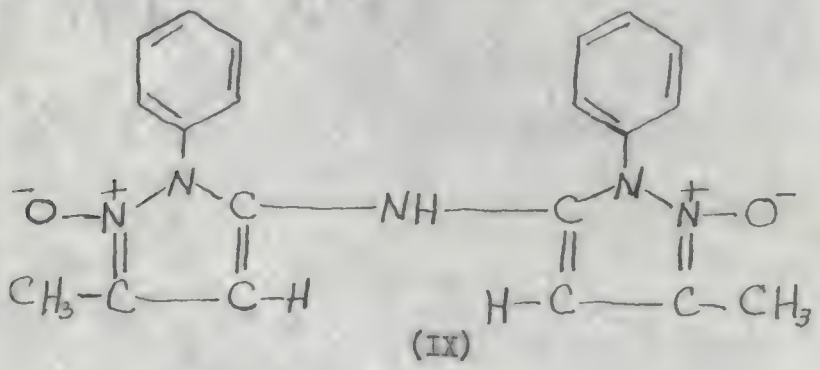


To be weaker requires that the crotonamide structure was a poorer electron sink than the benzene ring. This seemed reasonable because an amide carbonyl has relatively low conjugating power, and therefore this spectrum was considered to support the α -oxide structure.



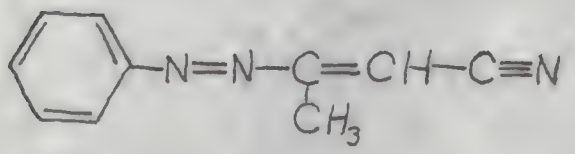
Attention was next turned to the white compound which certainly was not aminopyrazole from consideration of melting point alone, but appeared to be an intermediate product in the formation of (X). The Kuhn-Roth C-Methyl number was determined for the white compound, and the results indicated two methyl groups (Table 1). Carbon, hydrogen, nitrogen analysis indicated an empirical formula of $C_{30}H_{19}N_5O_2$ which was in agreement with the molecular weight determination of 336.6 (Theoretical 361) (Table 1). An infrared spectrum showed the following bands: one at 2.85μ characteristic of the N - H stretching of a secondary amine, one each at 6.22μ and 10.70μ characteristic of the pyrazole ring (Nonhebel and Chang, 16) bands at 6.05μ and 12.93μ characteristic of the $\overset{+}{N}-O^-$ group (see pages 9-13), and the expected carbon-hydrogen, carbon-carbon, and carbon-nitrogen bands. Notably, there were no bands at 6.16μ, 6.22μ and 11.93μ as with compound (VIII).

From a consideration of this data, it appeared that the white compound was the result of a condensation between two molecules of the starting amino pyrazole with the loss of one nitrogen atom. The infrared bands at 6.22μ and 10.70μ further indicated that the pyrazole rings remained intact in this condensation. In order to lose one nitrogen and retain the ring structure, the condensation must have occurred thru the amine nitrogen. Therefore, the structure (IX) was assigned to the white compound.



(IX)

This compound easily reacted with hydrogen chloride to form a white solid salt. Heating of this, either dry or in aqueous solution gave (VIII). Consideration of the mechanism of this reaction (page 22) led to a working hypothesis that (IX) would probably split to form an azo nitrile (X). The azo nitrile hydrazide (VIII) then would result from hydrolysis and oxidation of this nitrile.



(X)

A convenient way to check such a system appeared to be thru the related ester which has been described by Sander (3) and Nef (13). In the procedure described by Nef, ethyl aceto acetate phenylhydrazone was treated with mercuric oxide to obtain the desired compound phenyl-β-acetyl crotonate. It was noted that (X) resembled the phenyl-β-acetyl crotonate in structure and it was decided that this method of Nef might be used with diacetonitrile phenylhydrazone (VI) to obtain (X). When the product from this reaction was isolated, it was found to be a light brown solid melting at 105-107°C. This was then purified by sublimation under high vacuum at 80°C, and a white crystalline material was obtained melting at 109°C. From infrared spectrum the following bands were obtained: one at 4.45μ characteristic of the nitrile group, one at 6.20μ characteristic of a conjugated carbon-carbon double bond, a band at 6.25μ characteristic of an azo nitrogen-nitrogen group, and the other expected bands for carbon-hydrogen, carbon-nitrogen and carbon-carbon. Significantly, no bands were found in the N - H region for amines or amides, at 6.0μ or 10.7μ

for the pyrazole ring or at 6.83μ and 12.9μ for the $\overset{+}{N}-\bar{O}$ group. From this information, it was decided that this white compound had the structure (X) and that it was probably azipyrazole.

It was noted previously that (VIII) and (IX) were probably intermediates in the formation of azipyrazole. Furthermore, it was also found that (VIII) could be formed from (IX). It now seemed desirable to show that (VIII) could be converted to the azipyrazole (X). Cuhial (14) had used phosphorous trichloride in chloroform as the agent to reduce pyridine-1-oxides to the parent pyridines. In this reaction the oxygen was taken up by the phosphorous trichloride to form phosphorous oxychloride and it was thought that this oxychloride might react further with (VIII) to dehydrate the amide group to the necessary nitrile. When this reaction was run on (VIII) a light brown solid was obtained. This solid was sublimed and a white crystalline solid was obtained melting at 109°C. This was proven identical to (X) by mixed melting point (108-109°C).

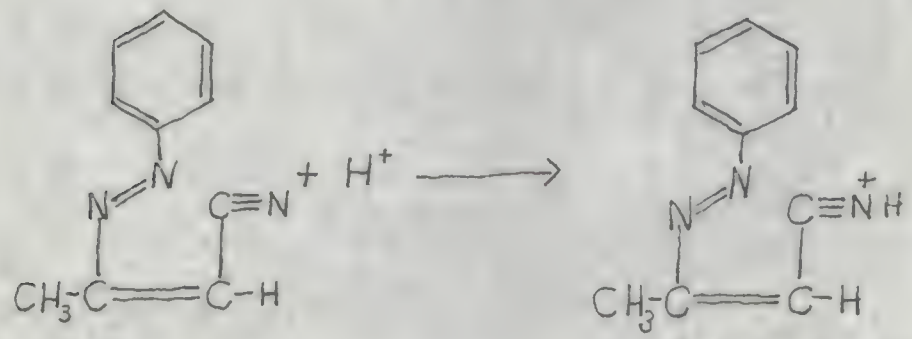
It was now felt that (X) was the correct structure for the azipyrazole. But in order to prove this beyond doubt, another method of synthesis was proposed which was independent of the method used by Michaelis (9). It had been shown that 3-(benzenesazoxy)-crotonamide (VIII) could be converted to azipyrazole (X) and it therefore seemed probable that 3-(benzeneazo)-crotonamide could be dehydrated to (X).

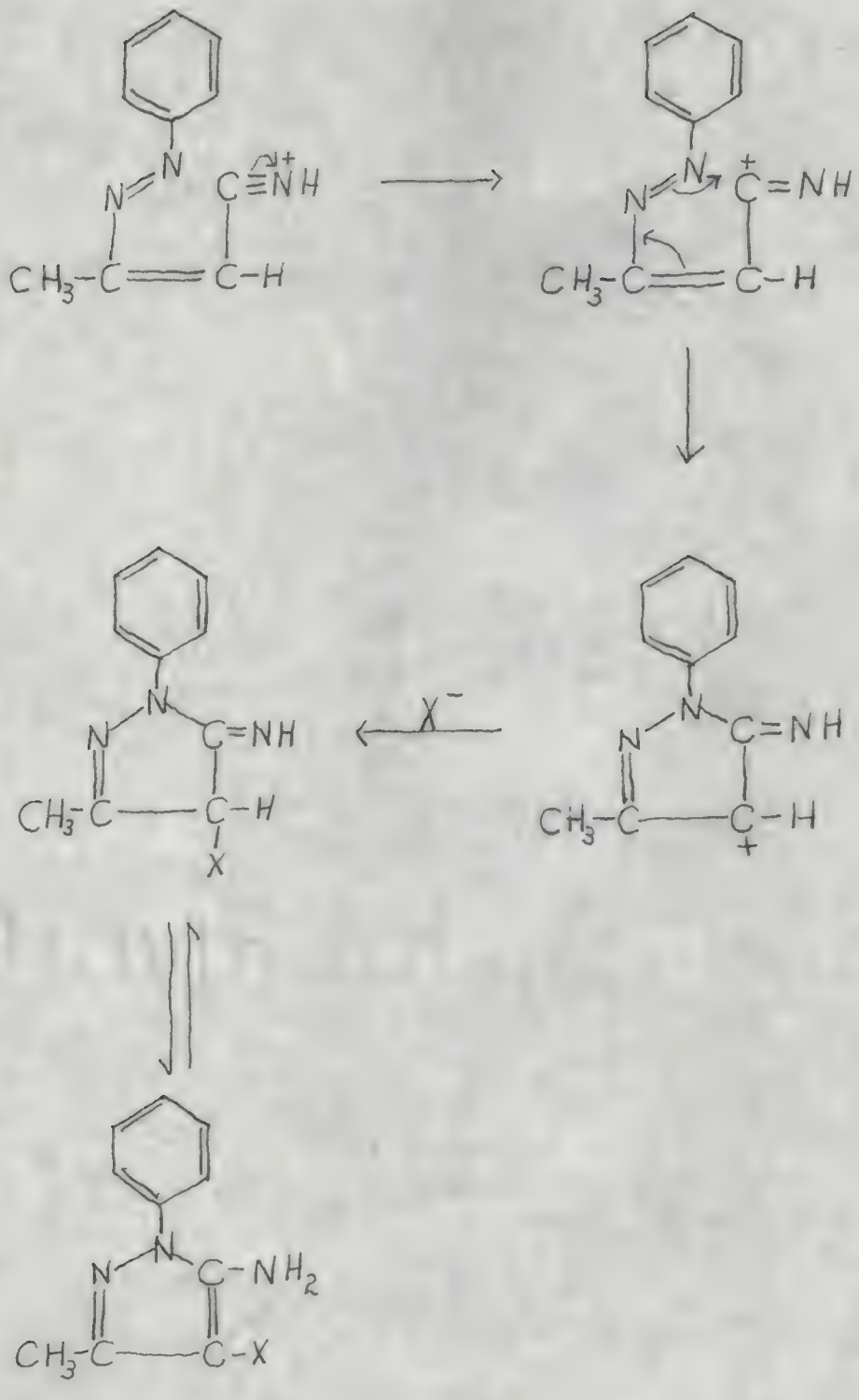
Once again the method of Kaf (13) was used to prepare ethyl 3-(benzeneazo)-crotonate (XI). This ester was then converted to the 3-(benzeneazo), crotonamide (XII) by means of liquid ammonia. When (XII) was treated with phosphorous pentoxide, a brown solid was isolated which after sublimation gave a white crystalline solid melting at 109°C and gave a mixed melting point of 109°C

with (X).

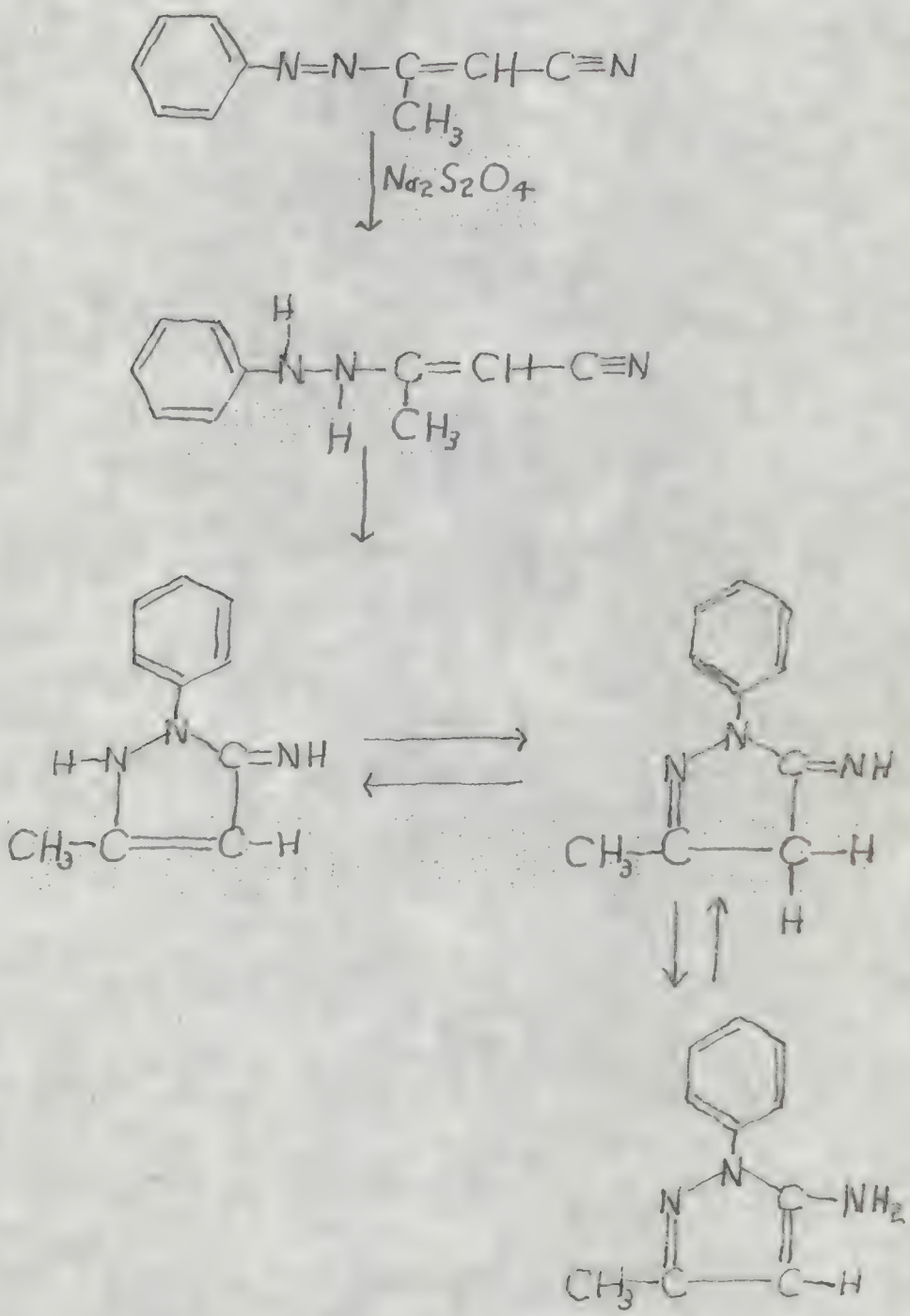
To relate the acids 5-oxide (VIII) to this independent method for making azipyrazole, (XII) was treated with monoperphthalic acid, (Behme, 4) in ether solution. Brown needles were isolated which were proven identical with (VIII) by mixed melting point (113°C).

As a result of the foregoing work, a formula for azipyrazole was determined that fitted the analytical data found by Michaelis. It was then necessary to show that this new formula could also fit the reactions with the hydrogen halides and sodium hydrosulfite. Concentrated hydrogen bromide was warmed with azipyrazole and a white solid isolated which melted at 105°C and had a mixed melting point of 83-99°C with the starting azipyrazole. This same reaction was carried out using concentrated hydrogen iodide and a white solid was obtained melting at 75°C. Both of these products agree with the products obtained by Michaelis. This reaction is novel in that it illustrates a new method for closing the pyrazole ring. The following mechanism has been suggested for this ring closure:



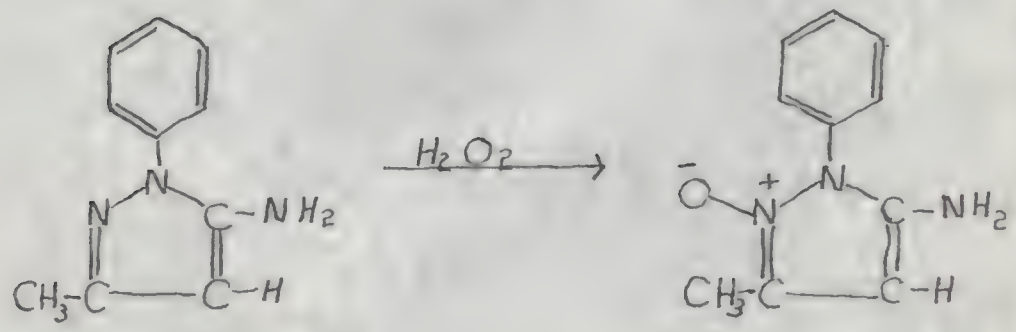


Conversion of [illegible]pyrazole to the 3-imino-5-methyl-2-phenylpyrazole by sodium hydrosulfite may also be explained by this structure for azipyrazole. This reagent is known to reduce azo linkage to hydrazo derivatives and then the ring would close as shown in the following mechanism:

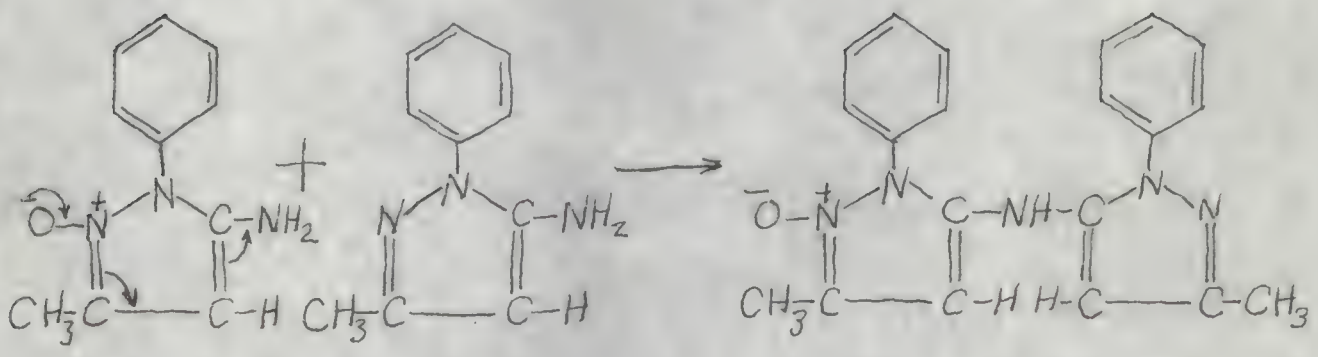


During the early part of this work, it was thought that the dimethyl aminopyrazole might be easier to prepare. The first step was to prepare diacetonitrile as described before. The reaction mixture was then treated with methyl iodide as described by Mohr (12). After the 1-methyldiacetonitrile was isolated, it was treated with phenylhydrazine base and the 1-methyldiacetonitrile phenylhydrazone was isolated. This phenylhydrazone was then cyclized with gaseous hydrogen chloride and the resulting hydrochloride was treated with 90 per cent hydrogen peroxide. A solid was isolated from this oxidizing mixture but was not investigated any further, as attention became focused at this time on the monomethyl compounds.

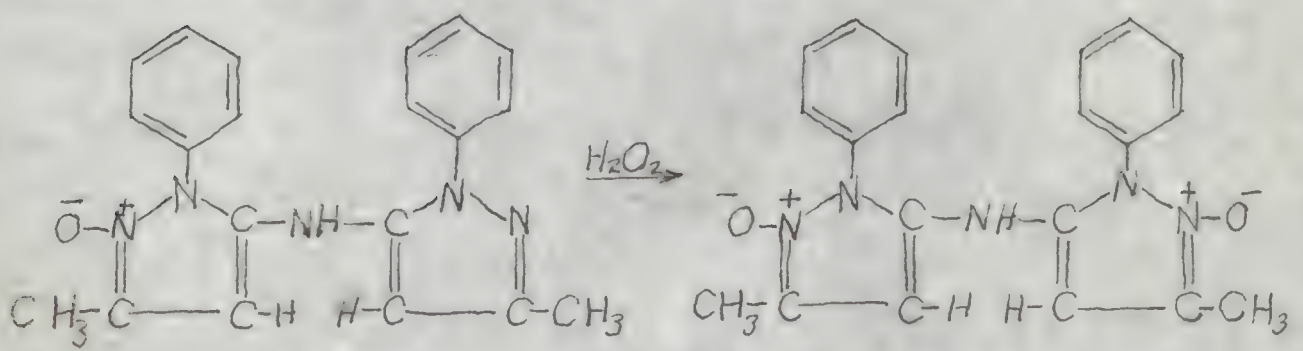
It has been shown how the new formula for aminopyrazole fitted the analysis and reactions given by Michaelis. However, in this work, two new compounds were found when the method of oxidation described by Michaelis was attempted. Since they were the only products formed, it was important to understand how their formation came about and the following mechanism is suggested. The first step is the formation of an N-oxide of the starting aminopyrazole. This was logical in that it was similar to the preparation of pyridine N-oxides. The oxygen forms a bond probably with the 1-nitrogen due to its greater basicity.



The oxygen then was able to feed electrons into the pyrazole ring with a result that the amino nitrogen became more negative and this could then add to a molecule of the imino pyrazole.

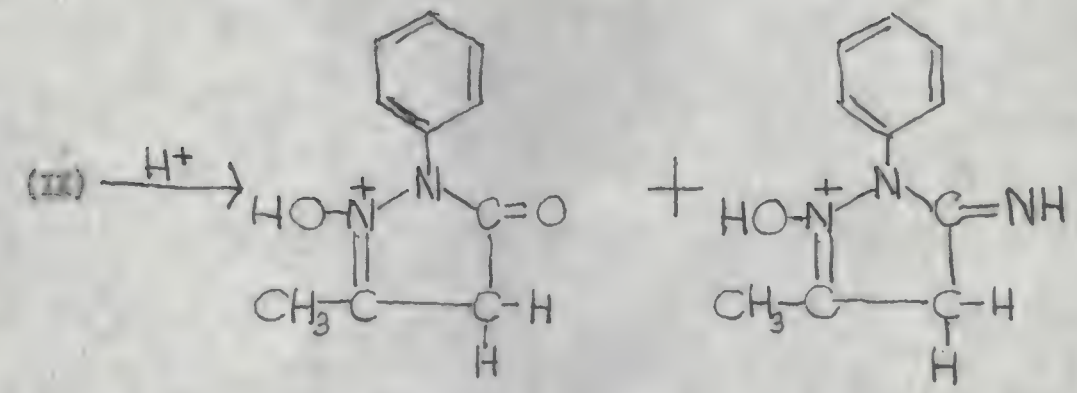


This product was then further attacked by hydrogen peroxide to give a second N-oxide function and the product (II) was formed.



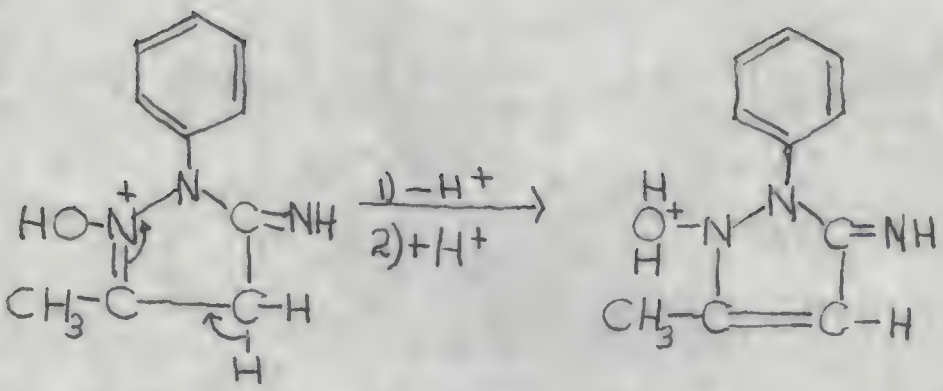
(IX)

Two routes were noted for the formation of (VIII). One route was from (II) which could under acid conditions exist in equilibrium with (XIII) and (XIV).

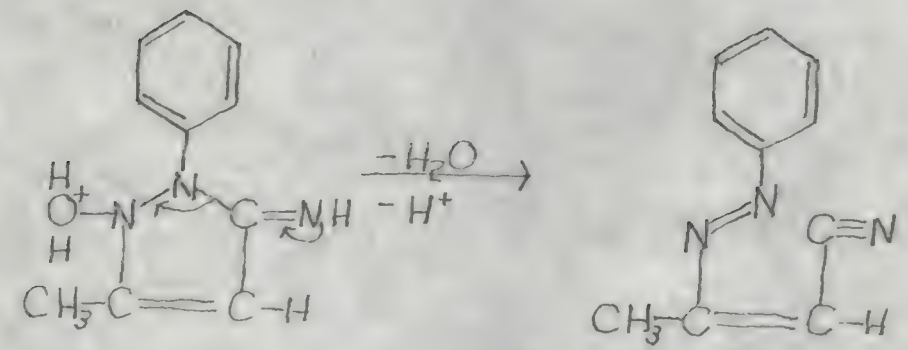


(XIII) (XIV)

(XIV) could lose a proton and then gain one on the OH grouping.

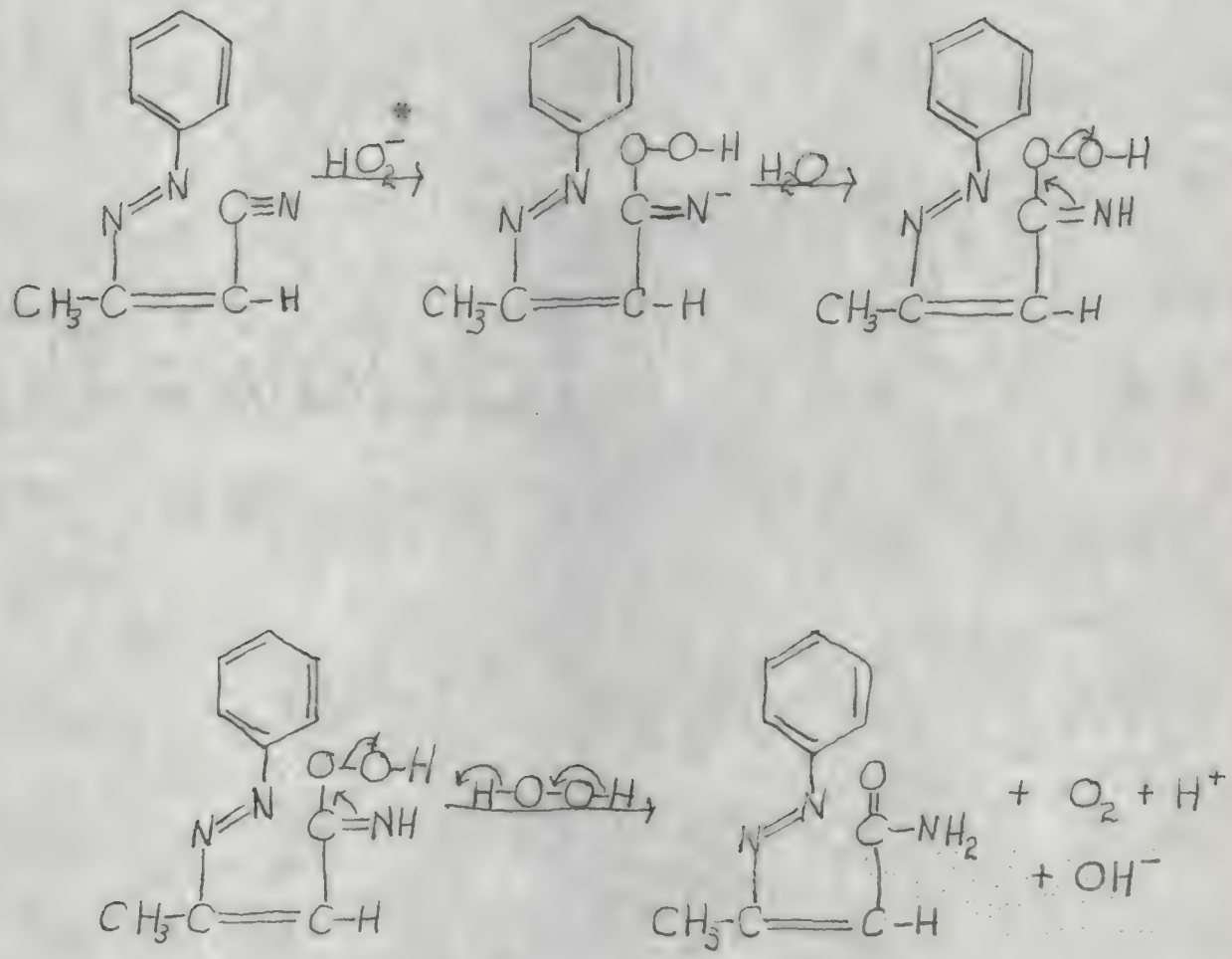


This intermediate could then lose a molecule of water and a proton and form antipyrenole (I).



(I)

However, the reaction would not stop here, but reacted further with hydrogen peroxide to form an amide. The mechanism for this reaction was known and was used here (Wiberg, 20).



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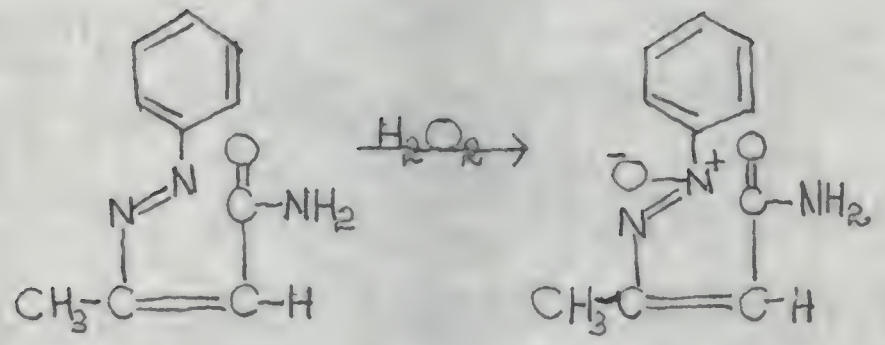
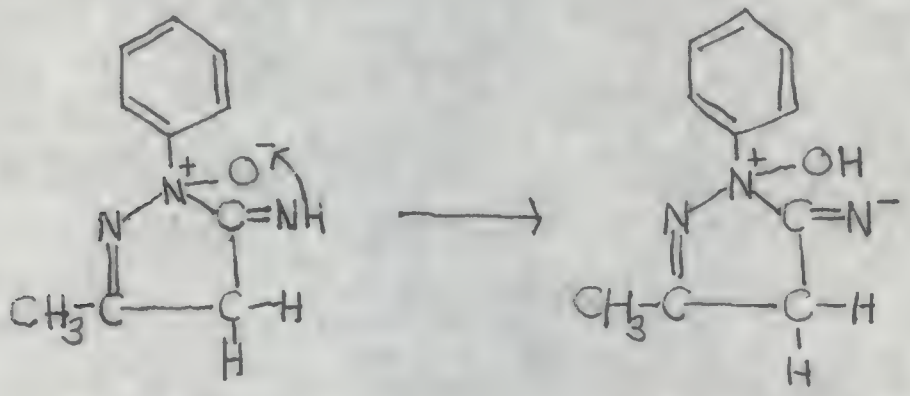
* From H_2O_2, which in turn may be formed by the reaction of (XIII) and water.

Finally, this amide was oxidized by hydrogen peroxide to form (VIII).

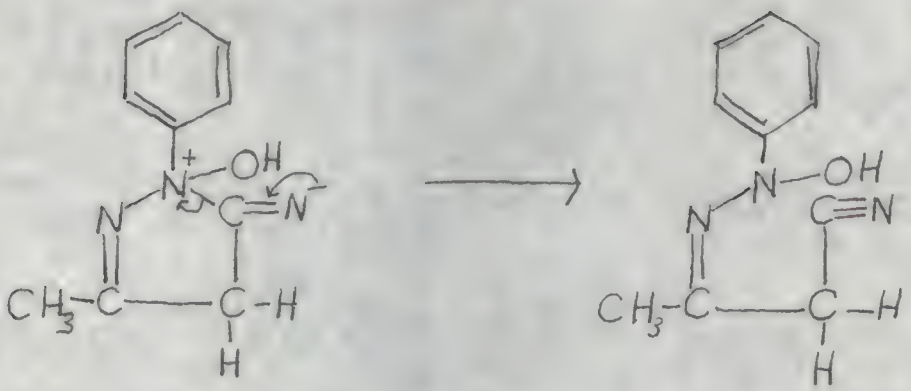


(VIII)

An alternate route for the formation of (VIII) involved the N-oxide of the starting imino pyrazole. In this mechanism the oxygen is on the 2-nitrogen. A proton is transferred from the imino group to the oxygen leaving the imino nitrogen with a negative charge.

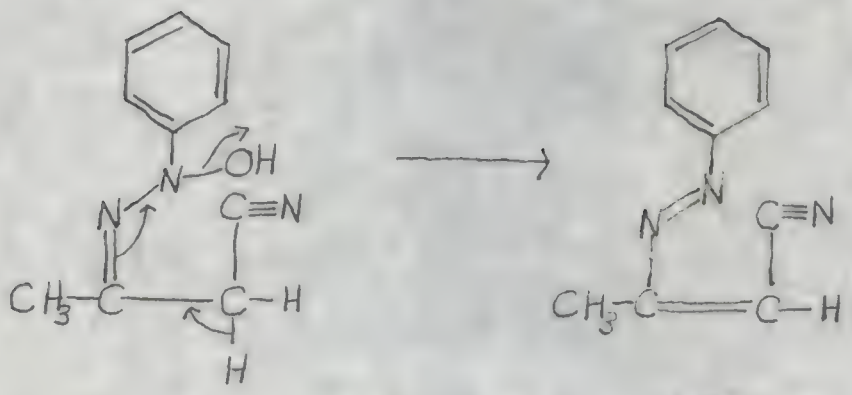


The pair of electrons from the imino nitrogen would shift and the ring band would break to form (XV).



(XV)

(XV) would then lose a proton and a hydroxyl ion, and by the shifting of electrons form (X). This would then react as before to form (VIII).



(X)

EXPERIMENTAL

Diacetonitrile (II)

Sodium sand was prepared by melting 77 gms. of sodium in xylene and shaking the molten sodium vigorously. After the xylene was decanted and replaced with dry benzene, 205 gms. (5.0 moles) of acetonitrile was added dropwise with stirring over a period of two hours. The temperature (inside the reaction flask) was maintained below 30°C for best yields. The reaction mixture stood for 24 hours and was then refluxed for two hours. Water was added to destroy any unreacted sodium, after which the benzene layer was decanted and distilled off leaving a reddish-brown oil. A three volume excess of benzene was added along with one volume of Skelly B, and on cooling with scratching a yellow solid formed melting at 52-53°C. Literature mp. 52-53°C (Holtzmart, 8). Yield: 64.7 gms. (16 per cent).

Diacetonitrile Phenylhydrazone (VI)

Sixty-four and seven tenths gms. (.709 moles) of (V) was mixed with 85.2 gms. (.789 moles) of phenylhydrazine base in a mortar and while grinding, 147 ml. of 30 per cent acetic acid was slowly added. The solid was filtered, and after recrystallization from ethanol, melted at 93-95°C. Literature mp. 97°C (Burns, 5). Yield: 87 gms. (63.6 per cent).

3-Amino-5-Methyl-2-Phenylpyrazole (VII)

Eighty seven gms. (.50 moles) of (VI) was dissolved in 250 ml. of absolute ethanol, and gaseous hydrogen chloride was bubbled in until saturated. The mixture was cooled, filtered and the solid dissolved in water. Gaseous ammonia

was bubbled until saturated and the white solid filtered. Melting point of (VII): 112-114°C. Literature: 115-116°C (Walther, 18). Yield: 65.4 gms. (75.1 per cent).

3,3'Bis-(5-Methyl-2-Phenylpyrazole)-Amine-1,1'-Dioxide (IX)

Five gms. (.029 moles) of (VII) was dissolved in a 50 per cent water-acetic acid solution. Three ml. of hydrogen peroxide was added and the solution was heated. A yellow crystalline solid precipitated, was filtered and recrystallized from a pyridine-water solution giving a white crystalline solid melting at 229-230°C. Yield: 3.57 gms. (33.6 per cent). Anal. calculated for $C_{20}H_{19}N_5O_2$: C, 66.46; H, 5.26; N, 19.39. Found: C, 66.47; H, 5.30; N, 19.36.

3-(Benzeneazo)-Crotonamide-N-Oxide (VIII)

Hydrochloric acid was added to a small portion of (IX) and a white hydrochloride separated mp. 178-180°C. This was heated at 160°C and the red oil left was recrystallized from dilute alcohol, giving a brown solid mp. 113°C.

Five gms. (.029 moles) of (VII) was dissolved in 35 ml. of concentrated hydrochloric acid and 3 ml. of 30 per cent hydrogen peroxide was added. The solution was evaporated to a red oil in a steam cone and the red oil recrystallized from dilute alcohol, giving a brown solid melting at 113°C. Additional product was obtained by extracting the dilute alcohol solution with ether and evaporating off the ether. Yield: 2.37 gms. (37.9 per cent). Anal. calculated for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.5. Found: C, 58.22; H, 5.42; N, 19.8.

(VIII) was also prepared by treating a small portion of (VII) with 90 per cent hydrogen peroxide in glacial acetic acid solution. The solution was

evaporated to a red oil on a steam cone and extracted with ether. When the ether was evaporated off, (VIII) was obtained melting at 113°C. Mixed melting point with above was 113°C proving the two were identical.

β-(Benzeneazo)-α-cyanoacrylic (Antipyrazole) (X)

The procedure of Ref (13) was used. One gm. (.0057 moles) of diazocinnamic phenylhydrazone was dissolved in 35 ml. of absolute alcohol. Two gms. (.0092 moles) of yellow mercuric oxide was added and the mixture refluxed for an hour. The free mercury was filtered off and most of the alcohol distilled off. Water was added and the mixture was extracted with ether which was distilled off leaving a red oil. This red oil was washed three times with Skelly B and then with ether and the ether evaporated off. From this ether extract was obtained a light brown solid melting at 103-107°C. This was sublimed under high vacuum (0.1 mm.) at 80-85°C giving a white crystalline solid melting at 109°C. Literature melting point 109°C (Michaelis and Schäfer, 11). Yield: 0.2 gm. (25.3 per cent). Anal. calculated for $C_{10}H_9N_3$: N, 24.55. Found: N, 24.22.

Conversion of (VIII) to (X)

The procedure of Ochiai (14) for removal of the oxygen from pyridine-N-oxides was used. Four hundredths gm. (.0002 moles) of (VIII) was dissolved in 2.5 ml. of ice cold chloroform, .05 ml. of phosphorous trichloride was added and the mixture refluxed for one hour at 70-80°C. The solution was cooled, 25 ml. of water added, made alkaline with aqueous sodium hydroxide and extracted with chloroform. This extract was dried with anhydrous sodium sulfate and the chloroform was evaporated under vacuum over sulfuric acid. A light brown solid

was recovered which gave a white crystalline material when sublimed under vacuum, melting at 109°C. This was proven identical with (X) by mixed melting point (108-109°C). Yield: 0.01 gms. (30 per cent).

Ethyl Acetoacetate Phenylhydrazone

The procedure of Ref (13) was used. Twenty-six gms. (0.2 moles) of ethyl acetoacetate was dissolved in a three volume excess of ether with cooling in an ice bath. Twenty-one and six tenths gms. (0.2 moles) of phenylhydrazine base was added and then the ether evaporated under vacuum over sulfuric acid. An oily red solid was isolated which turned light brown on drying and melted at 90°C. Literature melting point 90°C (Ref. 13). Yield: 18.2 gms. (41.9 per cent).

3-(Benzeneazo)-Ethyl Crotonate (XI)

Nine and one tenths gms. (.042 moles) of ethyl acetoacetate phenylhydrazone was treated with 12.96 gms. (.061 moles) of yellow mercuric oxide. A red solid melting at 90°C was isolated. Literature melting point 91°C (Ref. 13). Yield: 0.9 gms. (10 per cent).

3-(Benzeneazo)-Crotonamide (XII)

Eight hundredths gms. (.0003 moles) of (XI) was dissolved in absolute ethanol in a Carius tube. Gaseous ammonia was passed into the tube which was cooled in an acetone-dry ice mixture and the tube was sealed and heated at 110 C for ten hours. The solution was allowed to evaporate leaving a black crystalline solid melting at 74°C. Yield: 0.06 gms. (91.1 per cent). Anal. calculated for $C_{10}H_{11}N_3O$: N, 22.22. Found: N, 21.92.

Dehydration of (XII) to (X)

A small portion of (XII) was dissolved in benzene and a 1.5 mole excess of phosphorous pentoxide was added. The mixture was refluxed for thirty minutes, cooled, and the benzene solution filtered off and evaporated under vacuum over sulfuric acid. The solid obtained was sublimed and a white solid melting at 109° C was isolated. Mixed melting point with (X) showed them to be identical.

Monoperphthalic Acid

The method of Braun (4) was used. Fifty ml. of 15 per cent sodium hydroxide was cooled to -10° C in a three-necked flask and 21 ml. of thirty per cent hydrogen peroxide at -10° C was added with rapid stirring. The mixture was recooled to -10° C and 15 gms of finely powdered phthalic anhydride was added in one portion. When the anhydride had dissolved, 30 ml. of 20 per cent sulfuric acid cooled to -10° C was added. This solution was filtered through glass wool into a separating funnel and extracted once with 100 ml. of ether and three times with 50 ml. portions of ether. The ether extracts were combined and washed with three 30 ml. portions of 10 per cent ammonium sulfate. The ether solution was dried 24 hours over 10 gms. of anhydrous sodium sulfate. Concentration of monoperphthalic acid was 5×10^{-3} moles in 30 ml. of ether solution.

Preparation of (VIII) from (XII)

Five ml. of the ether solution of monoperphthalic acid was added to 0.04 gms. (.00021 moles) of (XII) and the mixture stood for two days. The phthalic

acid was neutralized with sodium hydrogen carbonate and the solution extracted with ether. The ether was dried over anhydrous sodium sulfate and evaporated in a vacuum over sulfuric acid leaving a brown solid melting at 113°C. This was shown to be identical with (VIII) by mixed melting point (113°C). Yield: .01 gm. (23.3 per cent).

2-Picoline-3-Oxide

The general method of Ochiai (14) was used. Forty gms. (0.43 moles) of 2-picoline, 150 ml. of glacial acetic acid, and 35 ml. of 30 per cent hydrogen peroxide was heated at 70-80°C for three hours, after which 18 ml. more of 30 per cent hydrogen peroxide was added and the mixture heated for 16 hours more at 92°C. The solution was cooled, the acetic acid was neutralized with potassium hydroxide, and the solution extracted with benzene. The benzene was taken off under water vacuum and the product was then distilled under vacuum. The 2-picoline-3-oxide boiled at 102-104°C at 7.5-8mm. Literature 123-124°C at 15mm. Yield: 25 gms. (53.5 per cent).

2-Methyl-3-Imino Butyronitrile

Diacetonitrile was prepared as described previously. The method of Weiss was then used to methylate the diacetonitrile (Wiberg,30). 205 gms. (4.9 moles) of acetonitrile was used in the Thorpe reaction. The reaction mixture was refluxed for two hours and 225.6 gms. (1.58 moles) of methyl iodide was added over a period of one hour. The reaction mixture stood for three hours after which it was refluxed for one and one-half hours and then filtered while hot. Yellow needles precipitated from the benzene solution on cooling which melted at 105°C. These were purified by dissolving in water, extracting with ether,

and removing the ether to give brown needles melting at 125°C. Additional products were obtained by concentrating the benzene solution. Yield: 38.7 gms. (8.2 per cent). Literature melting point 122-125°C (Wiberg, 20).

2-Methyl-Butyronitrile-3-Phenylhydrazone

Five gms. (.052 moles) of 2-methyl-3-imino butyronitrile was treated with an acetic acid solution of 5.63 gms. (.052 moles) phenylhydrazone base and the solution concentrated. The solid was filtered and dried. Melting point 93-94°C. Yield: 5.9 gms. (61.5 per cent).

3-Amino-4,5-Dimethyl-2-Phenylpyrazole Hydrochloride

Seventy-three hundredths gms. (.0037 moles) of 2-methyl butyronitrile-3-phenylhydrazone was dissolved in absolute alcohol and gaseous hydrogen chloride was bubbled in until saturated. Filtered the solid hydrochloride. Yield: .32 gms. (37.8 per cent).

3-Amino-4-Cyano-5-Methyl-2-Phenylpyrazole

A small portion of 3-(benzeneazo)-crotonitrile (aminopyrazole) was treated with 40 per cent hydrobromic acid and warmed. The solution was saturated with alkali and extracted with ether and the ether removed leaving a white solid melting at 105°C. Literature melting point 108.5°C (Michaelis, 9). Mixed melting point with starting aminopyrazole 83-97°C.

3-Amino-4-Iodo-5-Methyl-2-Phenylpyrazole

The same procedure was used as with the bromo compound. Melting point of the product isolated, 75°C. Literature melting point 75°C (Michaelis, 9).

General Procedure for Kuhr-Roth C-Methyl Numbers

The oxidising solution was prepared by adding 25 ml. of sulfuric acid (sp. gr. 1.84) to a solution of 16.8 gms. chromic anhydride (CrO_3) in 100 ml. of distilled water. Exactly 5 ml. of this solution was added to the samples (10-20 mg., see Table 1) and the reaction mixture was refluxed from a cold finger for one and five tenths hours at 130°C. The solution was cooled, the cold finger replaced by a still head and the acetic acid was steam distilled, 30 ml. of the distillate being collected. The distillate was treated with .1002N sodium hydroxide to the phenolphthalein end point. The results are in Table 1.

Molecular Weight Determinations

The Rast method was used. The depression constant of the camphor used was found to be 326. A Thiele tube and ordinary thermometer were employed for determining the melting points. The results can be found in Table 1.

Dielectric Constant and Dipole Moment Determination

The standing microwave technique (Haugen, 7, and Von Hippel, 17) was used in taking the data for determining the dielectric constants. The dipole moment was calculated from this and the calculated molar refraction (Volkenberger, 19). The value obtained was .65 Debye units.

Infrared Measurements

All infrared spectra was run on a Perkin-Elmer Model 12 single beam, double pass spectrometer. A salt prism was employed for the general spectra and a lithium fluoride prism was used in observing the amide and amine N-H

bands. The significant bands have been noted previously.

Ultraviolet Measurements

The UV spectra noted were taken on a Beckman Model DU Quartz Spectrophotometer.

SUMMARY

Aminopyrazole was described in the early part of this century by Michaelis and his co-workers as a structure proposed. Various reactions were run on this compound and the results fitted to the proposed structure. However, in the light of present day chemical knowledge, the results noted by Michaelis cannot be explained using his proposed structure.

Numerous attempts were made to prepare aminopyrazole using the method described by Michaelis. However, all these attempts gave two compounds (VIII) and (IX) both of which contained two oxygen atoms. The structures of these compounds were determined and shown to be related to aminopyrazole, by converting (IX) to (VIII) and then (VIII) to the aminopyrazole. A compound which appeared to be aminopyrazole was prepared by the reaction of yellow mercuric oxide with diacetonitrile phenylhydrazone (VII), and by converting phenyl-β-amino ethyl orthonate (XI) to the corresponding amide (XII), followed by dehydration with phosphorous pentoxide. Furthermore (XII) was tied in with the related compounds converting it to (VIII) with monoperphthalic acid.

From this data, the correct structure of aminopyrazole was shown to be 3-(benzenesazo)-crotonitrile (X).

ACKNOWLEDGMENT

The author wishes to thank Dr. Louis D. Ellsworth of the Department of Physics for his aid in determining the dielectric constant and dipole moment, Dr. Basil Curnutte for his calculations of the vibrational spectra bands of pyridine-N-oxide and his aid in interpreting the infra spectra taken, and Dr. Scott Searles, who directed this work, for his encouragement and assistance in every way during this project.

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THE STRUCTURE PROOF OF AZIPYRAZOLE

by

WILLIAM ROBERT MINK, JR.

B. S., Beloit College, 1954

AN ABSTRACT

OF A THESIS

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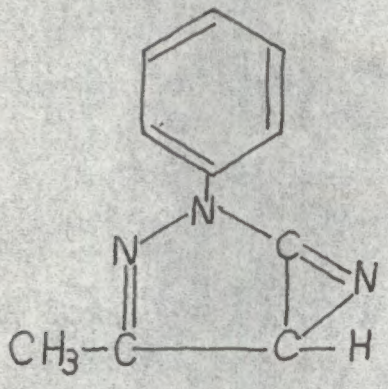
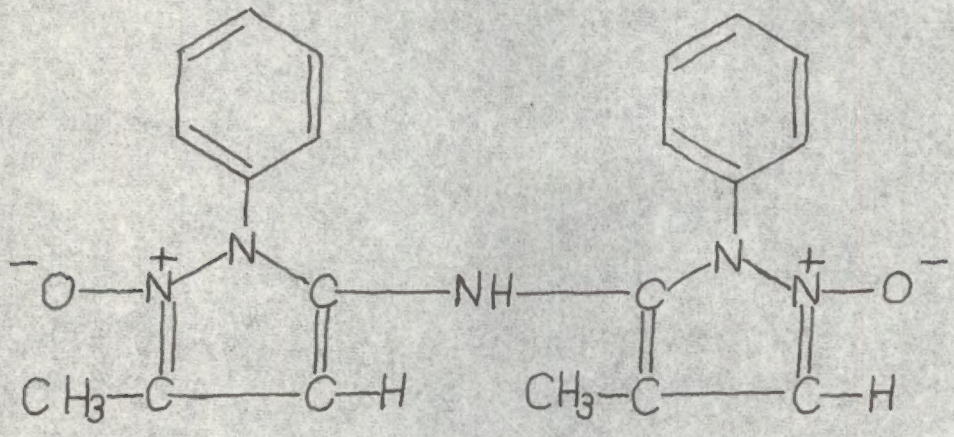
The oxidation of 2-aryl-3-aminopyrazoles with the loss of two hydrogens and the formation of a peculiar 3-4 fused bicyclic system (I) was reported by Michaelis and his co-workers to be rather general.

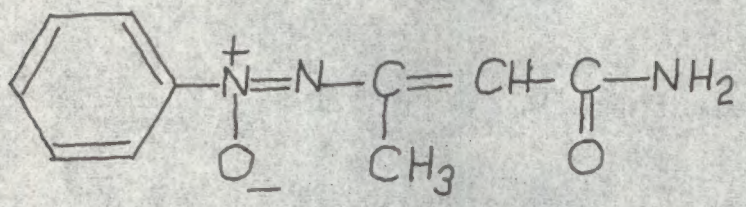


The general name azipyrazole was applied to these compounds, and the name itself was applied to the compound with Ar = phenyl, R_1 = methyl and R_2 = hydrogen. The internal strain of such a system, however, seems prohibitive, and therefore reinvestigation of the structure was undertaken.

The preparation of azipyrazole most recommended by Michaelis and co-workers failed to give azipyrazole but instead gave a dipyraylamine-N, N^1-dioxide (II).

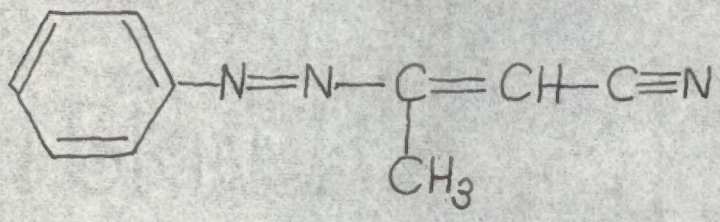


Heating the hydrochloride of this gave a compound with physical properties very similar to those reported for azipyrazole, but the analysis and infrared spectrum indicated it to be an amide N-oxide, probably 3-(benzeneazoxy)-crotonamide (III).

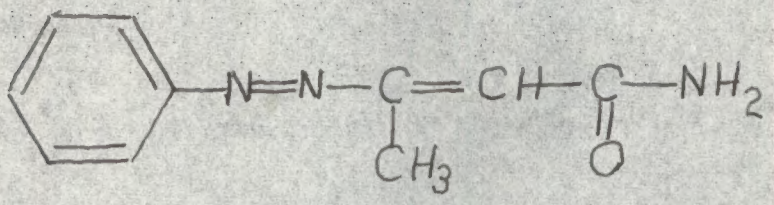


The assignment of the N-oxide structure was initially based on infrared studies of known N-oxides of different types. This resulted in the establishment of certain infrared absorption bands for the $\overset{+}{N}\!-\!O^{-}$ band, which will be of general use in future identifications of such compounds.

The formation of azipyrazole was accomplished by standard reactions: namely, removal of the oxygen with phosphorous trichloride followed by dehydration with the phosphorous oxychloride formed. It had the melting point reported by Michaelis and the infrared spectrum and analysis were in agreement with the 3-(benzeneazo)-crotonitrile (IV).



The structure was verified by an independent synthesis. A closely related compound, ethyl-3-benzeneazo crotonate, was known to be formed by the oxidation of ethyl acetoacetate phenylhydrazone with mercuric oxide. Its preparation was repeated and it was found to be converted to the amide (V) by ammonolysis.



Treatment of this amide with monoperphthalic acid gave the amide N-oxide originally obtained, while dehydration gave azipyrazole. A simplified route to azipyrazole was found by treatment of diacetonitrile phenylhydrazone with mercuric oxide.

Mechanisms for the formation of benzazo crotonic acid derivatives from aminopyrazoles were discussed. An explanation for the easy formation of aminopyrazoles by cyclizations of the 3-(benzeneazo)-crotonitrile with acids and reducing agents was also advanced.